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The protective effect of various typhus fever vaccines in man and the course of the disease following immunization.

by Dr. Erwin Ding

Zeitschrift f. Hygiene u. Infektionskr. 124: 670-682 (1943).

During the course of the three winters of 1940-1943, extensive observations were made of typhus fever among groups of male persons. Physicians, nurses, soldiers and civilians were among the patients. The commitment of immunized personnel occurred with their consent in areas and activities in which the contact with typhus fever and the infecting lice was particularly close, and with a high degree of probability conducive to the disease.

In the treatment of the material, the patients were grouped into non-immunized and immunized persons, according to the various vaccines. Only those persons were chosen, whose date of infection could be clearly established. The size of the groups was almost identical, permitting a comparison with each other. Those cases that had appeared among non-vaccinated persons in the same locality, at the same time and under identical external conditions, were designated as "normal typhus fever" (control groups I and II). It is significant that the clinical course of the two groups, separated by time and space, in part revealed extensive differences, a phenomenon which had been pointed out by Krugowsky (1) and others with considerable emphasis.

The average age of all observed persons is shown in table 1.

The observed persons, with an average age of 33.2 years for group I and 31.2 years for group II, were committed 6-8 weeks after the last immunizatio Prior contact with typhus exanthemicus was out of the question. They were well nourished and rested, and free of intercurrent diseases.

Type and tolerance of the utilized vaccines.

Within the two groups of typhus fever patients mentioned above, we used a number of different vaccines for the purpose of active human immunization, produced from killed strains of Rickettsia prowazeki and R. mooseri. A detailed presentation of the production methods may be omitted in view of the published literature.

Vaccine IA was produced from the intestines of lice with strains of R. prowazeki, according to Weigl's method, as modified by Eyer (2). It was used in concentrations of 17, 33 and 50 intestines per 1 ccm.

Vaccine IB, produced by Gildemeister and Haagen (3) of the Robert Koch Institute, Berlin, based on the method of Cox and Otto-Wohlrab. In this vaccine, pure strains of R. prowazeki from Eastern Europe were utilized, whereby one yolk sac yielded 25 ccm vaccine per chicken egg.

Vaccine IC "weak," produced by the Behring Works Marburg (Lahn), based on the method of Otto and Mohlrab (4). In cultures on embryonated egg yolk sacs, strains of R. mooseri and prowazeki were mixed. One egg was expanded into 450 ccm vaccine. This vaccine is no longer being produced.

Vaccine IC "strong" was produced in the same manner as IC "weak," but expanded to only 250 ccm. This vaccine therefore has almost twice as many rickettsia as IC "weak." (No longer being manufactured).

Vaccine IIA was developed and produced by Giroud (5) in the Pasteur Institute, Paris, from rabbit lungs with strains of R. prowazeki from Eastern Europe and North Africa (*). Approximately 1 liter typhus fever vaccine was obtained from one rabbit lung weighing 35-50 g.

Vaccine IIB was produced in Roumania according to data furnished by Combiescu, Zotta, Manilescu, Pop and Tascau (6). Canine lungs were used as rickettsial carriers in this vaccine.

(*) Footnote: Personal communication from Prof. Giroud (strain "Tunis-Katza and Warsaw 13").

Tolerance of the vaccines.

The tolerance of the vaccines was generally favorable and did not exceed the level heretofore known about immunization with typhus vaccines. The strongest relative manifestations were caused by the vaccine after Weigl (Fig. 1).

Manifestations, especially after the second injection, included local erythema, tumescence and slight infiltrations, occasionally increased temperatures up to 37.8°C. These signs disappeared after about 8-10 hours, except for the infiltrations which remained palpable for several days. The best tolerance was observed in connection with pulmonary vaccines, which left about 3/4 of the immunized persons without symptoms. The remainder again revealed local erythema, light swellings and low-grade elevations in temperature. Vaccines IB, IC "weak" and IC "strong" left about ½ without change in the general condition and without local symptoms. The remaining 50%, in addition to redness, swellings and slight elevations in temperature to 37.6°C, in isolated cases had headache, vomiting and inflammation of the conjunctiva, as well as light diarrhea. The ability to work was not hindered in any case.

In all observed cases, one complete protective immunization had been carried out at three different times. Persons who had received repeated inoculations were not admitted to comparison.

Clinical course of typhus fever among non-immunized and protected personnel.

The clinical picture of typhus fever among immunized and non-immunized persons was very carefully observed in connection with the two diseased groups.

The incubation time of typhus fever is set at 11-14 days by Juergens (7). Schittenhelm (8), in connection with his own illness, calculated a period of 13 days for the eruption of the disease.

According to our own observations, considerably shorter periods of incubation were also noted by the practising physicians. In the wake of a laboratory accident, 3 persons fell ill with typhus caused by strain "Katelska" (*) (R. prowazeki from the Robert Koch Institute Berlin), known for its extremely high virulence in guinea pig experiments. All three had not been immunized and were most certainly free of lice. The fourth person whose anamnesis will be retold in abbreviated form (see below), infected himself with a lancet covered with a strain of R. prowazeki in chicken egg culture. This patient had received an inoculation with Weigl's vaccine from the typhus research institute of the Army in Krakow three months previously.

(*) Footnote: Personal communication from Prof. Gildemeister.

1. H.A., 41 years old. 48 hours ago infection with typhus fever virus. Immediate admission to the infectious ward. Prot. OX 19 agglutination neg.

Findings: Well nourished and strong. Skin and visible mucous membranes moderately suffused. Temp. 37.7°C. Pulse 132, conjunctivitis, sensitivity to light, puffy face, spleen not palpable. Blood pressure after RR 120/80.

Course. On the 9th day after infection, eruption of the exanthema, becoming hemorrhagic on the 12th day. Spread also to the palms. On the 21st day, disappearance of the exanthema. Prot. OX 19 agglutination on the 12th day 1:400 +, on the 19th day 1:12,800 +. Depression of the blood pressure from the 10th day to 85/50. Blood picture: leukocytosis, in the second week, values around 20,000. On the 4th day increase in staff cells to 12%. On the 19th day, abatement of fever, Pulse 110; during the fever, delirious conditions lasting for days, with strong motor unrest. Routine convalescence. Diagnosis: Typhus fever.

2. L.A., 29. Frequently recurring gallstones. Rachitis in childhood. Pneumonia 10 years ago. -- 3 days ago, infection with typhus fever virus. Prot. OX 19 agglutination negative.

Findings: Well nourished and strong. Temp. 38.8°C; pulse 104. Blood pressure after RR 140/100. Strong sensitivity to light, conjunctivitis, stabbing headache, especially in the orbital cavities, leading to the occiput. Feeling of lassitude, calf pressure-sensitive, indicated stiffness of the neck.

Course: On the 7th day, eruption of a spotty, light red petechial exanthema on the thighs and trunk. Isolated, small, pale red spots on the hands. Blood pressure diminished to 95/55, systolic sounds over the coronary apex. The patient appears seriously ill. During stronger motor unrest (as if counting money), especially toward evening -- attacks of mania. Fever rises to 40°C. On the 16th day critical abatement of fever to 35.9°C. Death at 20:15. Blood pressure since the 8th day down to 95/55. On the 16th day 80/50. Pulse beats initially elevated up to 110, since the 14th day severe bradycardia with

pulse around 60. Blood picture in the 1st week, slight leukocytosis from 7 to 81,000, increase in staff cells, from the 5th day to 20%. On the 11th day Prot. OX 19 agglutination 1:200. -- Diagnosis: Failure of coronary circulation with typhus fever.

3. P.A., 27. Has never been seriously ill. 48 hours ago infection with typhus fever virus. Prot. OX 19 agglutination negative.

Findings. Severe headache toward evening, tongue coated, puffy face (face of a red wine drinker), severe sensitivity of the calves to pressure, knee jerk and patellar reflex pronounced. Temp. 38.2°C; pulse 98. Spleen palpable.

Course. Following the temperature elevation on the 2d day, normal temp. of 36.8°C toward the morning of the 3rd day; steep increase to 40.6°C during the afternoon, continuing until the 16th day. On the 17th day critical abatement, followed by normal temperatures. On the 8th day after infection, eruption of bluish-red roseola on the thighs and the abdomen, some also on the trunk. On the 10th day the roseola become hemorrhagic. The skin between the individual roseola is reddish. From the 20th day on, disappearance of the exanthema. Severe involvement of the central nervous system, stupefaction, some loss of hearing, diplopia. This disappears only 10 days after the abatement of fever. A slight impediment to hearing is still demonstrable 3 months after defervescence. On the 11th day Prot OX 19 agglutination 1:400 +, on the 18th day 1:600, 14 days after defervescence still 1:6800. Since the 6th day, lowered blood pressure around 80/60, elevation to 100/70 since abatement of fever, attaining values of 120/90 3 weeks after defervescence. Initial pulse acceleration to 110; the pulse has returned to normal values of 70-80 beats per minute since defervescence. Stubborn catarrh of the bladder during convalescence.-- Diagnosis. Typhus fever.

4. E.D., Dr. med., 30. No previous serious illnesses. On the 3rd day after infection with typhus fever virus, malaise, light headache, especially above the eyes. Temperature 38.2°C; on the 4th day nearly symptomless. On the 5th day, temp. elevation to 38.9°C, severe headache, especially behind the eyes, conjunctivitis and sensitivity to light, puffy lids; calves and thighs sensitive to pressure, also the musculature of the shoulder zone. Skin of the trunk especially sensitive to touch. Quite isolated roseola on both flanks. Admission to the hospital toward evening.

Course. Moderately severe typhus fever with temp. elevation to 39.5°C. Very slight involvement of the central nervous system (no stupor other than extraordinarily severe headaches). Circulation RR 90/50 lasting 3 weeks. On the 12th day, critical abatement of fever. Pulse elevated to 100 for some time. During convalescence, tendency to fainting spells, otherwise symptomless. Prot. OX 19 agglutination in the 2d week 1:800 +. Diagnosis: Typhus fever with preceding immunization.

In the observed group infections, the incubation times of group I (non-vaccinated) ranged between 2 and 5 days, of group II (non-vaccinated) between 2 and 10 days. The greatest frequency of the disease's commencement was seen on the 2d and 3rd day in the non-immunized groups (table 2).

The available material presented a clear picture to the effect that a particularly severe course could be expected following a very short incubation time. All cases with incubation times up to 5 days are to be considered as moderately severe to severe, where strong involvement of the central nervous system (delirium, paralysis, cerebral vomiting) and the circulation occupied the foreground. Outspokenly light disease forms were not observed in connection with such short incubation times. It is possible that a very massive infection with typhus fever pathogens may lead to a particularly rapid breaching of the physical defenses and then causes an extraordinarily severe clinical course. According to our material, this assumption seems to be supported, since all fatal cases in the non-vaccinated groups had shortened incubation times of 2-5 days.

With previous immunization, the incubation times, while lengthened in comparison with non-vaccinated groups (cf. table 2), are still considerably shorter than generally assumed. With the exception of groups IIB with 4 and 5 days, the eruption of the disease in the other immunized groups is concentrated on the 6th-7th day after infection.

The commencement of the illness in the non-immunized groups I and II was marked by temp. elevation to 39-40°C, severe frontal headache, especially above the eyes; limb and muscle pains (calf), slight conjunctivitis with sensitivity to light, puffiness of the lids and low-grade catarrh of the respiratory tract. The symptomatology of these two groups coincided largely with the descriptions listed by Sonnenschein (9) and Walther (10) for the initial stages of typhus fever. On the other hand, the course of the initial stage was atypical in the immunized persons of the several groups. Temperature elevation to 37.8°C, light headache, as well as a certain malaise were also present, but could not be evaluated as characteristic typhus fever symptoms due to their insignificance. We agree with the experiences gained by Eyer et al. (11), in that a minimum of symptoms are evident in the morning hours, which reappear, however, within 2 hours after getting up. The mildest manifestations -- just as later in the clinical course -- were evoked by vaccines IA, IB and IIA. Somewhat stronger initial symptoms were observed in connection with vaccines IC "weak" and IC "strong." These, too, showed a distinct attenuation of initial manifestations vis-a-vis the control groups.

The duration of the temperature elevations in the non-vaccinated groups I and II at 17 and 18 days (table 3) agrees in principle with that given for typhus fever by Schittenhelm (8) and other authors.

On the other hand, considerable deviations appeared in connection with immunized persons, in the duration as well as in the degree of fever. All immunized persons, with an average duration of 10-12 days, showed a curtailment by 5-7 days in comparison with the control groups. Here, the patients of vaccine group IB and IIA with 10 days, and IA with 11 days, showed an insignificant curtailment when compared to the Behring vaccines IC "weak" and IC "strong" and the canine lung vaccine IIB with 12 days; especially distinct is the remission shown by the mean curve of vaccine IIB after initial fever, pointed out first by Nicolle (12) and later by Mrugowsky. Löffler and Mooser (13) observed the same phenomenon in murine typhus. The degree of fever revealed the most favorable course in the mean curves (Fig. 2) of vaccine

groups IA, IB and IIA, in which the 39°C mark was not exceeded. Groups IC "weak", IC "strong" and IIB also showed a very distinct attenuation of the fever compared to the control groups. It is found, therefore, that, according to the observed material, an immunization against typhus fever favorably influences the duration and degree of fever.

The value of immunization is shown less clearly with respect to the circulation. No significant differences are found between the compared groups, with an average depression of the blood pressure to 85/55 mm Hg after 4d (table 4).

Concerning the pulse, it may be said that it regains its normal values somewhat earlier after immunization than without this measure (Fig. 2). In screening the entire material, it was determined that no important effect of vaccination on the pulse was observed at the apex of the disease, in contrast to convalescence.

On the other hand, the effect of vaccination seems to be of particular value in regard to the central nervous system. While the central nervous system was very strongly involved in the non-immunized groups I and II, comparable to the descriptions of Juergens (7), our material showed time and again that the vaccinated typhus patients made a far healthier impression in comparison with non-vaccinated persons. The involvement of the CNS manifested itself by headache, partly slowed speech, frequent muscular twitching of the face, insomnia at night, pronounced sleepiness during the day, partly with motor unrest --- here, too, with a distinct attenuation vis-a-vis unvaccinated patients.

Strong disturbances of the sensorium were noted only in connection with vaccine groups IC "weak" and IC "strong." In one case difficulty of hearing and delirium developed. Here these symptoms persisted for only 2-4 days, while their duration in non-vaccinated groups amounted in part to up to 2 weeks.

The effect of vaccination on the duration and degree of exanthema seems noteworthy. It became visible in full strength on 100% of the observed typhus patients belonging to the control groups. In the first group the cutaneous alterations persisted for 13 days on the average, in the second for 16 days.

In contrast, the exanthema was visible for only 6.8-8.4 days on the average in all groups of immunized patients (table 5). The quality of the exanthema was also different. The roseola generally did not hemorrhage. In no case was the skin between the individual roseola diffusely reddened. Here, too, we can agree in principle with the experiences gained by Eyer et al. The action of the exanthema was changeable, however, in respect to its appearance. In most cases it erupts all at once, but in about 1/3 of the cases it appeared in several small waves. The individual vaccines show the following reaction concerning the severity and appearance of exanthema:

Vaccine IA. 58% of the patients showed a distinct exanthema, lasting for an average of 7.2 days. It was indistinct, rapidly disappearing, in 13%. 20% remained free of visible cutaneous alterations.

Vaccine IB. 54.5% had exanthema persisting for an average of 7 days. 11% showed indistinct, rapidly disappearing cutaneous alterations. 34.5% remained unaffected.

Vaccine IC "weak." In 91% of the patients distinct exanthema persisted for 8.3 days. 6% showed rapidly vanishing, indistinct manifestations on the skin. 3% remained unaffected.

Vaccine IC "strong." The exanthema was visible in 70.4% of the patients for an average of 8.4 days. 17.6% remained free of exanthema; 12% had a quickly vanishing, washed-out eruption.

Vaccine IIA. In 55% of the typhus fever patients, exanthema lasting for an average of 6.8 days was observed. 30% had rapidly vanishing, indistinct cutaneous symptoms; 15% remained free.

Vaccine IIB. In 60% of the patients, distinctly visible exanthema was present, lasting for 7.5 days on the average. 25% revealed ephemeral manifestations on the skin; 15% remained without a visible eruption.

The red blood picture showed no noteworthy deviations from the norm.

On the other hand, the action of the white blood cells was variable in all inoculated and non-inoculated groups. Especially during the 2d week of illness, the total leukocyte count slowly rose to values between 10,000 and 20,000. Maximal leukocytes were seen about 3-5 days after the highest temp. (table 6). Within the individual classes of the white blood count, a shift took place among the neutrophils toward the staff cells, which usually are strongly increased in the first week of illness. According to Schilling (14), normal blood contains 4% staff cells. We saw up to 15% in our material. Similar and higher values were found by Lampert (15) and Dawidowskie (16) in his extensive Russian material. Leukopenia, as described by Loeffler and Mooser for typhus exanthemicus with a Mexican murine strain, was not seen by us in connection with strains of Rickettsia prowazeki.

A difference in the blood picture between immunized and non-immunized typhus patients cannot be determined.

Complications occurred, other than in the control groups I and II, only in vaccine groups IC "weak," IC "strong" and IIB. Of these, 70% were bronchopneumonia; among the other 30%, diphtheria, urticaria and parotitis were diagnosed.

The average weight loss in the individual groups did not show significant variations (table 8). It amounted to an average of 7.4 and 8.1 kg in the non-vaccinated control goups, 5.2 and 6.4 kg in the inoculated groups. It ought to be dependent in part on the degree and duration of fever.

The serologic reaction of the observed cases of typhus fever was according to the manual in 84% of the control groups in respect to the Prot. OX 19 agglutination. The failure of this method has been discussed elsewhere (17).

For external reasons, the Prot. OX 19 agglutination was continuously and methodically controlled only in the control groups I and II and the vaccine groups IIA and IIB, while the other groups were subjected to blood tests only for the purpose of securing a diagnosis. In vaccine group IIA, the Prot. OX 19 agglutination remained negative or "below the threshold" (17) up to the 10th day, i.e. it only attained values of 1:100 ∕. In the following days the titer rose to 1:1600 in the majority of patients, persisting to the end of the 3rd week, to decrease slowly far into convalescence.

Similar action was seen in the group inoculated with vaccine IIB. Here, in 3 cases, a "gross flocculation of the saline control in form of snow flakes" was observed (17), which could not be explained satisfactorily.

The convalescence of the observed typhus fever patients in all vaccinated groups was distinctly shortened in comparison to the non-vaccinated control groups. The circulation recovered more rapidly, the pulse returned to the norm sooner, the symptoms on the part of the CNS disappeared completely in the first two weeks.

Mortality in control group I amounted to about one third, in group II to one fifth. The greatest cause of death by far was to be found in the failure of the circulation.

No deaths occurred in vaccinated groups IA, IB, IIA and IIB. One person each died in groups IC "weak" and IC "strong". After a survey of our typhus fever material, it may be said that an immunization against typhus fever confers far-reaching protection against a fatal course of the disease. In this connection, even strongly diluted vaccines such as IC "weak" and IC "strong", consisting of mixtures of murine strains and prowazeki, led to favorable conditions of immunity.

Summary.

The tolerance and effect of various vaccines was tested among two large groups infected with typhus fever, the material being obtained from louse intestines, egg yolk cultures, rabbit and canine lungs. The following results were obtained:

I. The incubation time of typhus fever may be considerably shorter than heretofore assumed. By inoculation, fever was depressed, the duration of the fever was shortened, and the entire course was considerably alleviated with respect to the central nervous system and the circulation.

II. The immunization protects against death in the overwhelming majority of cases. It does not seem to decrease morbidity.

III. The newer vaccines from egg yolk sac cultures, rabbit and canine lungs are suitable in typhus fever. According to our experience, they are as effective as those from louse intestines, if obtained from pure strains of R. prowazeki.

IV. Even vaccines with mixtures of strains of R. mooseri and prowazeki considerably attenuate the course of typhus fever.

V. The white blood picture was carefully observed in all groups. It shows a strong increase in staff cells. A difference between immunized and non-immunized typhus fever patients cannot be deduced from the blood picture.

Tables.

Table 1. Average age (Impfstoffgruppe - vaccine group, Vergl. Gruppe - control group).
Table 2. Incubation times of the various groups (patients in %; days of maximum frequency are framed). Erkrankungstag - day of falling ill.
Table 3. Average fever. In Tagen kürzeste und längste Fieberdauer - shortest and longest duration in days. Durchschnitt in Tagen - average in days.
Table 4. Average decrease in blood pressure.
Table 5. Average duration of exanthema.
Table 6. Movement of leukocytes and staff cells in typhus fever, average.
Table 7. Complications in % of patients.
Table 8. Average weight loss.

Graphs.

Fig. 1. Vaccine tolerance.


total number of immunized persons


with symptoms


without symptoms

(1, 2, 3 = 1, 2 or 3 shots)

Fig. 2. Average pulse and temperature.